Docket No.: 04654/1200494-US1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Balasubramanian GOPALAN et al.

Application No.: 10/821,642 | Confirmation No.: 9007

Filed: April 9, 2004 | Art Unit: 1626

For: NOVEL HETEROCYCLIC COMPOUNDS USEFUL FOR THE TREATMENT OF INFLAMMATORY AND ALLERGIC DISORDERS: PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM | Examiner: Y. L. Chu

CLAIM FOR PRIORITY AND SUBMISSION OF DOCUMENTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby claim priority under 35 U.S.C. 119 based on the following prior foreign application filed in the following foreign country on the date indicated:

Country	Application No.	Date
India	363/MUM/2003	April 11, 2003

In support of this claim, a certified copy of the said original foreign application is filed herewith.

Dated: April 28, 2006

Respectfully submitted,

By _____

Jay P. Lessler
Registration No.: 41,151
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

बौध्दिक सम्पदा भारत
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PROPERTY **INDIA**
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GEOGRAPHICAL INDICATIONS

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तोडी इस्टेट, 3 री मंजिल, सन मिल कंपाउंड, लोअर परेल (प.), मुंबई - 13
Todi Estate, 3rd Floor, Sun Mill Compound
Lower Parel (West), Mumbai – 400 013

दूरभाष Tel 022-2492 4058
022-2492 5092
022-2496 1370
022-24949845
022-24922710
फॅक्स Fax 022-2495 0622
022-24903852
Email patmum@vsnl.net
Website www. ipindia.nic.in

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Patent Application and Provisional Specification filed on 11/04/2003 in respect of Patent Application No.363/MUM/2003 of **Glenmark Pharmaceuticals Limited,** an Indian company having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026 INDIA.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 29th day of December 2005.

(RAKESH KUMAR)
ASSTT.CONTROLLER OF PATENTS & DESIGNS.

FORM 1
THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2),7 and Rule 33A)

We, Glenmark Pharmaceuticals Limited, an Indian company having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026 INDIA hereby declare

1.(a) that we are in possession of an invention titled **"NOVEL HETEROCYCLIC COMPOUNDS USEFUL FOR THE TREATMENT OF INFLAMMATORY AND ALLERGIC DISORDERS: PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"**

(b) that the provisional specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

2. further declare that the inventors for the said invention are **GOPALAN BALASUBRAMANIAN, LAXMIKANT ATMARAM GHARAT, AFTAB DAWOODBHAI LAKDAWALA, USHA KARUNAKARAN** All citizens & residents of India belonging to Glenmark Pharmaceuticals Limited , B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026

3. that we are the assignee of the true and first inventors

4. that our address for service in India is as follows;

Glenmark Pharmaceuticals Limited
Plot No.A-607, T.T.C Industrial Area
M.I.D.C., Mahape
Navi Mumbai – 400 709
INDIA

5. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed) _____
GOPALAN BALASUBRAMANIAN

(Signed) _____
LAXMIKANT ATMARAM GHARAT

(Signed) _____
AFTAB DAWOODBHAI LAKDAWALA

(Signed) _____
USHA KARUNAKARAN

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. following are the attachments with the application
(a) Provisional Specification (40pages, in triplicate)
(b) Fee Rs. 5000.00 (five thousand rupees only) in bank draft bearing No. 008924 dated 10 February, 2003 drawn on UTI Bank Ltd

We request that a patent may be granted to us for the said invention

Dated this (Eleventh) 11th day of April 2003

CHERYL PINTO
Director
Glenmark Pharmaceuticals Limited

To,
The Controller of Patents
The Patents Office Branch. Mumbai

Thriplicate
25/mum-ltr0/2003
363/mum/2003
11/04/2003

FORM 2

THE PATENTS ACT 1970
(Act 39 of 1970)

PROVISIONAL SPECIFICATION

(SECTION 10)

NOVEL HETEROCYCLIC COMPOUNDS USEFUL FOR THE TREATMENT OF INFLAMMATORY AND ALLERGIC DISORDERS: PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Glenmark Pharmaceuticals Limited, an Indian Company,
registered under the Indian company's Act 1957 and
having its registered office at

B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road
Post Box No. 26511
Mumbai - 400 026, India

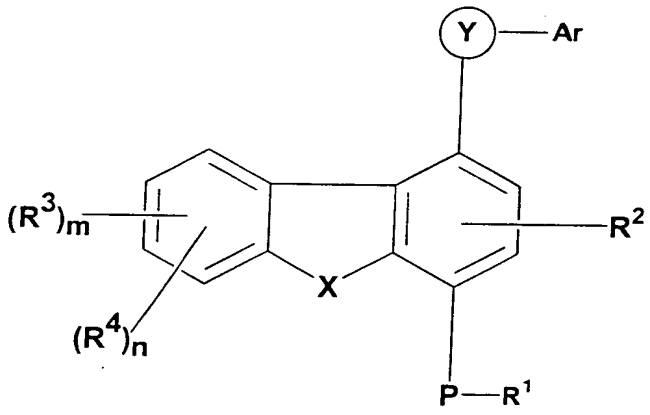
THE FOLLOWING SPECIFICATION DESCRIBES THE NATURE OF THE INVENTION

363/mum/2003
11.04.2003

Field of the Invention

The present invention relates to novel heterocyclic compounds, their analogs, their tautomers, their regioisomers, their stereoisomers, their enantiomers, their diastereomers, their polymorphs, their pharmaceutically acceptable salts, their appropriate N-oxides, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them. The present invention more particularly relates to novel Phosphodiesterase type 4 (PDE4) inhibitors of the formula (1), their analogs, their tautomers, their enantiomers, their diasteromers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their appropriate oxides, their pharmaceutically acceptable solvates and the pharmaceutical compositions containing them.

The invention thus relates to compounds of the formula (1)



(1)

wherein:

R^1, R^2 and R^3 may be same or different and are independently selected from the groups consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or

unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, protecting groups, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^a$, $-S(O)_q-R^a$, $-S(O)_q-NR^aR^a$, $-NR^aR^a$, ,$-OR^a$, $-SR^a$ or when two R^3 substitutents ortho to each other, may be joined to a form a saturated or unsaturated ring, which may optionally include up to two heteroatoms which may be same or different selected from O, NR^a or S;

wherein R^4 represents $-NR^5R^6$ or $-C(=L)-R^5$; in which R^5 and R^6 may be same or different and are independently selected from the groups consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^a$, $-S(O)_q-R^a$, $-S(O)_q-NR^aR^a$, $-C(=NR^a)-R^a$, $-C(=NR^a)-NR^aR^a$, $-C(=S)-NR^aR^a$, $-C(=S)-R^a$, $-N=C(R^aR^a)$, $-NR^aR^a$, $-OR^a$, $-SR^a$, protecting groups or R^5 and R^6 to each other may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms which may be same or different selected from O, NR^a or S;

Ar is substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclic ring or substituted or unsubstituted heteroaryl ring;

Preferably Ar is optionally substituted phenyl, optionally substituted pyridyl or optionally substituted pyridyl-N-oxide in which optional substituents (one ore more) may be same or different and are independently selected from the groups consisting of hydrogen, hydroxyl, halogen, cyano, nitro, carboxyl, trifluoroalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted amino or mono or di substituted or unsubstituted alkylamino

X is O, $S(O)_q$ or NR^a;

Y is $-C(O)NR^7$, $-NR^7S(O)_q$, $-S(O)_qNR^7$ or $-NR^7C(O)$; Wherein q is 0, 1 or 2;

R^7 is hydrogen, substituted or unsubstituted alkyl, hydroxyl, $-OR^a$, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic ring ;

wherein P represents O , S;

wherein m represents 0 – 3;

wherein n represents 1 – 4;

wherein L represents O, S or NR^a;

wherein q represents 0,1 or 2

Wherein R^a represents hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, protecting groups, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^a$, $-S(O)_q-R^a$, $-S(O)_q-NR^aR^a$, $-NR^aR^a$, $-OR^a$ or $-SR^a$;

with the provisos;

1) when R^5 is a hydrogen, the R^6 is not hydrogen;

2) when R^6 is a hydrogen, the R^5 is not hydrogen;

The present invention also relates to a process for the preparation of the above said novel heterocyclic compounds of the formula **(1)** as defined above. The compounds of general formula **(1)** more particularly, down regulate or inhibit the production of TNF-α as they are PDE4 inhibitors and therefore are useful in the treatment of variety of allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjuctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, diabetes, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. The compounds of the present invention are

particularly useful for the treatment of asthma and chronic obstructive pulmonary disease (COPD)

Back ground of the Invention

Airway inflammation characterizes a number of severe lung diseases including asthma and chronic obstructive pulmonary disease (COPD). Events leading to airway obstruction include edema of airway walls, infiltration of inflammatory cells into the lung, production of various inflammatory mediators and increased mucous production. The airways of asthmatic patients are infiltrated by inflammatory leukocytes, of which the eosinophil is the most prominent component. The magnitude of asthmatic reactions is correlated with the number of eosinophils present in lungs.

The accumulation of eosinophils is found dramatically in the lungs of asthmatic patients although they are very few in the lungs of a normal individual. They are capable of lysing and activating cells and destroying tissues. When activated, they synthesize and release inflammatory cytokines such as IL-1, IL-3, TNF-α and inflammatory mediators such as PAF, LTD4 and relative oxygen species that can produce edema, bronchoconstriction. Tumor necrosis factor (TNF-α) was also known to be involved in the pathogenesis of a number of autoimmune and inflammatory diseases. Consequently, manipulation of the cytokine signaling or biosynthetic pathways associated with these proteins may provide therapeutic benefit in those disease states. It has been well demonstrated that TNF-α production in pro-inflammatory cells becomes attenuated by an elevation of intracellular cyclic adenosine 3',5'-monophosphate(cAMP). This second messenger is regulated by the phosphodiesterase(PDE) family of enzymes. The phosphodiesterase enzymes play an integral role in cell signaling mechanisms by hydrolyzing cAMP and cGMP to their inactive 5' forms. Inhibition of PDE enzymes thus results in an elevation of cAMP and /or cGMP levels and alters intracellular responses to extra cellular signals by affecting the processes mediated by cyclic nucleotides. Since eosinophilis are believed to be a critical proinflammatory target for asthma, identification of the expression of PDE 4 gene family in eosinophils led to the PDE 4 as potential therapeutic target for asthma [Rogers.D.F.,

Giembycz.M.A., *Trends Pharmacol. Sci.*, 19, 160-164(1998); Barnes,P.J., *Trends Pharmacol.Sci.*, 19,415-423(1998)].

The mammalian cyclic nucleotide phosphodiesterases(PDEs) are classified into ten families on the basis of their amino acid sequences and/or DNA sequence, substrate specificity and sensitivity to pharmacological agents [Soderling,S.H., Bayuga,S.J., and Beavo,J.A., *Proc. Natl. Acad. Sci., USA*,96,7071-7076(1999); Fujishige, K, Kotera, J., Michibata, H., Yuasa, K., Takebayashi,Si, Okamura,K. and Omori,K., *J.Biol.Chem.*,.,274, 18438-18445(1999)]. Many cell types express more than one PDE and distribution of isoenzymes between the cells varies markedly. Therefore development of highly isoenzyme selective PDE inhibitors provide a unique opportunity for selective manipulation of various pathophysiological processes.

Phosphodiesterase type 4 (PDE4) is an enzyme which regulates activities in cells which lead to inflammation in the lungs. PDE4, a cAMP-specific and Ca^{+2}-independent enzyme, is a key isozyme in the hydrolysis of cAMP in mast cells, basophils, eosinophils, monocytes and lymphocytes. The association between cAMP elevation in inflammatory cells with airway smooth muscle relaxation and inhibition of mediator release has led to widespread interest in the design of PDE4 inhibitors[Trophy,T.J., *Am.J.Respir.Crit.Care Med.*, 157, 351-370(1998)]. Excessive or unregulated TNF-α production has been implicated in mediating or exacerbating a number of undesirable physiological conditions such as diseases including osteoarthritis, and other arthritic conditions; septic shock, ecdotoxic shock, respiratory distress syndrome, bone resorption diseases ; Since TNF-α also participates in the onset and progress of autoimmune diseases, PDE4 inhibitors may find tremendous utility as therapeutic agents for rheumatoid arthritis, multiple sclerosis and Crohn's disease. [*Nature Medicine*, 1, 211-214(19195) and *ibid.*, 244-248]. TNF-α is also reported to be a factor of insulin-resistant diabetes because it declines the phosphorylating mechanism of insulin receptors of muscle and fat cells [*J.clin.Invest.*, 94, 1543-1549(1994)].

Interest in the drugs capable of selective inhibition of PDE 4 has taken much attention due to several factors such as (a) the tissue distribution of PDE-4 strongly suggested that

the pathologies related to the central nervous and immune systems could be treated through the selective PDE 4 inhibitors (b) the increase in intracellular cAMP concentration, the obvious biochemical consequence of PDE-4 inhibition, has been well characterized in immuno-competent cells where it acts as a deactivating signal.

Recently four human cDNA isoforms of PDE-4 (PDE4-A,B,C,D) were identified. mRNA for all these four isoforms was expressed in human lungs. PDE 4-A, B and D were expressed in eosinophils. Of these gene families, PDE-4 characterized as the cAMP-specific gene family has been shown to predominate in pro-inflammatory human lymphoid and myeloid lineage cells.

It has been demonstrated that increasing cAMP levels within these cells results in suppression of cell activation which in turn inhibits the production and release of pro-inflammatory cytokines such as TNF-a. Since eosinophilis are believed to be a critical pro-inflammatory target for asthma, identification of the expression of PDE 4 gene family in eosinophils led to the PDE 4 as potential therapeutic target for asthma.

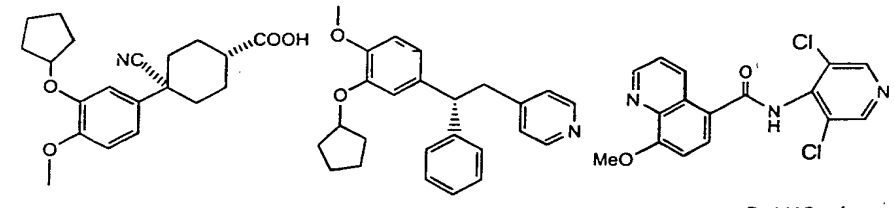
OBJECTIVE OF THE INVENTION

The usefulness of several PDE 4 inhibitors, unfortunately, is limited due to their undesirable side effect profile which include nausea and emesis (due to action on PDE4 in CNS) and gastric acid secretion due to action on PDE4 in parietal cells in the gut.[Barnette, M.S., Grous, M., Cieslinsky, L.B.,Burman,M., Christensen,S.B., Trophy,T.J.,*J. Pharmacol.Exp.Ther.*,273,1396-1402(1995)]. One of the earliest PDE4 inhibitor, Rolipram, was withdrawn from the clinical development because of its severe unacceptable side effect profile.[Zeller E.et.al.,*Pharmacopsychiatr.*, 17, 188-190(1984)]. It has recently become apparent, to some extent. The cause of severe side effects of several PDE4 inhibitor molecules in human clinical trials has recently become apparent.

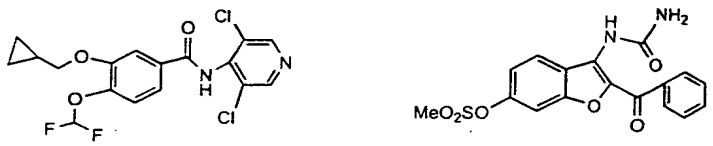
There exists two binding sites on mammalian PDE4 at which inhibitor molecules bind. Also PDE4 exists in two distinct forms which represent different conformations.

They are designated as High affinity Rolipram binding site PDE4H and Low affinity Rolipram binding site PDE4L[Jacobitz,S., McLaughlin,M.M., Livi,G.P., Burman,M., Trophy,T.J., *Mol.Pharmacol* .,50, 891-899(1996)]. It was proved that certain side effects (vomiting and gastric acid secretion) are associated with inhibition of PDE4H whereas some beneficial actions are associated with PDE4L inhibition. It was also found that human recombinant PDE4 exists in 4 isoforms A, B, C and D[Muller,T., Engels,P., Fozard,J.R., *Trends Pharmacol. Sci.*, 17, 294-298(1996)]. Accordingly compounds displaying more PDE4D isoenzyme selectivity over the A, B or C are found to have less amount of side effects than Rolipram [Hughes. B et.al.,, *Br. J. Pharmacol.* **1996**, 118, 1183-1191]. Therefore selective inhibitors of PDE4 isozymes would have therapeutic effects in inflammatory diseases such as asthma and other respiratory diseases.

Although several research groups all over the world are working in this direction for achieving the desired highly selective PDE4 isozyme inhibitors, so far the success is limited. Among the various compounds which showed clinically proven PDE 4 inhibition,



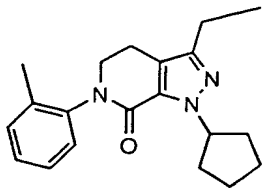
ARIFLO 2 CDP-840 3 D-4418 4



Roflumilast 5 Bay-19-8004 6

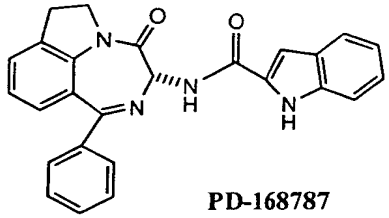
'Ariflo" of the formula 2(Smith Kline Beecham's compound), Byk Gulden's Roflumilast of formula 5 and Bayer's Bay-19-8004 of formula 6 have reached advanced stage of human clinical trials. Some of the other compounds which have shown potent PDE4 inhibitory activity are CDP-840 of the formula 3 (Cellthech's compond), D-4418 of the formula 4 (Schering-Plough's compound), 5CP-220,629 of the formula 7 (Pfizer's) , PD- 168787 of

the formula 8 (Parke-Davis's compound) and Filaminast of the formula 9 (American Home Products' compound). However, recently due to various reasons such as efficacy and side effects problems, Ariflo, CDP-840 and Bay-19-8004 were discontinued from clinical trials for asthma treatment. Other compounds of the formulae 4 and 7 are presently undergoing phase-1 clinical trials.



CP - 220,629

7



PD-168787

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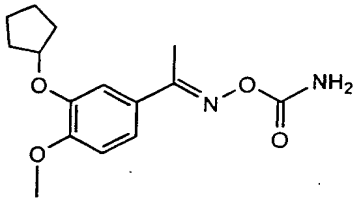


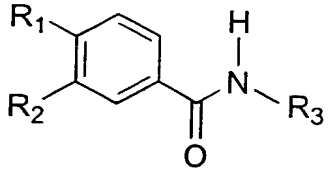
Filaminast

9

During the course of our research aimed at the development of novel anti-asthmatic compounds having potential PDE4 inhibitory activity, we have filed a WTO patent application in India bearing No. 922/MUM/2002 dated October 23, 2002 for a novel series of tricyclic compounds useful for the treatment of inflammatory and allergic disorders and subsequently we continued our research to get the potent PDE4 inhibitors, in this connectgin we have found in the literature,

1) US 5,712,298 granted patent (Issued on January 27, 1998 to BYK Gulden Lomberg Chemische Fabrik GmbH.,)

The invention relates to compounds of formula I,



(I)

In which,

One of the substituents R1 & R2 is hydrogen, 1-6C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy,benzyloxy or 1-4C-alkoxy which is completely or partially substituted by fluorine, and the other is 1-4C alkoxy which is completely or partially substituted by fluorine, and

R3 is phenyl, pyridyl, phenyl which is substituted by R31, R32 and R33 Or pyridyl which is substituted by R34, R35, R36 and R37 where,

R31 is hydroxyl, halogen, cyano, carboxyl, trifluoromethyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonyloxy, amino, mono- or di- 1-4C-alkylamino or 1-4C-alkylcarbonylamino,

R32 is hydrogen, hydroxyl, halogen, amino, trifluoromethyl, 1-4C-alkyl, 1-4C-alkoxy,

R33 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy,

R34 is hydroxyl, halogen, cyano, carboxyl, alkyl, amino, 1-4C-alkoxy, 1-4C-alkoxycarbonyl or amino,

R35 is hydrogen, halogen, amino, amino, or 1-4C-alkyl,

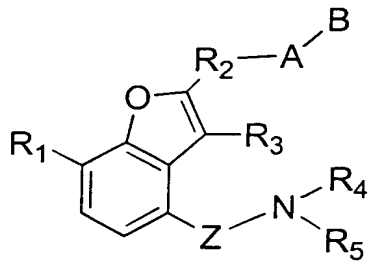
R36 is hydrogen or halogen and,

R37 is hydrogen or halogen,

The salts of these compounds and N-oxides of the pyridines and their salts.

2) PCT Patent publication WO 99/40085 (published on August 12, 1999 by Darwin Discovery Ltd.)

According to the invention the compounds are of formula (I);



(I)

Wherein;

Z is CO or CS;

R_1 is OH, alkoxy optionally substituted with one or more halogens or thioalkyl optionally substituted with one or more halogens;

R_3 is H, alkyl, halogen;

R_4 is H or alkyl;

R_5 is aryl or heteroaryl either of which may be substituted at any position with (one or more) substituents R_{14} or alkyl-R_{14};

R_{14} is alkyl optionally substituted with one or more halogens, aryl, heteroaryl, heterocycle, CO_2R_8, $CONR_9R_{10}$, $SO_2NR_9R_{10}$, OR_{11}, halogen, CN, NR_8R_{12}, COR_{13}, $S(O)_pR_{13}$ or $NHSO_2CF_3$;

P is 0-2;

R_8 is H, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclo, cycloalkylalkyl, arylalkyl, heteroarylalkyl, or heterocycloalkyl;

R_9 and R_{10} are the same or different and are H, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclo, cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl or NR_9R_{10} represents a heterocyclic ring;

R_{11} is H, alkyl(optionally substituted with one or more halogens), cycloalkyl, aryl, heteroaryl, heterocyclo, cycloalkylalkyl, arylalkyl, heteroarylalkyl, or heterocycloalkyl;

R_{12} is is H, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclo, cycloalkylalkyl, arylalkyl, heteroarylalkyl, or heterocycloalkyl, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl, alkylsulphonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl;

R_{13} is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclo, cycloalkylalkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_2 is alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl or heterocycloalkyl, any of which is attached at any position on the alkyl portion to A and (through the same or different position) to the benzofuran ring wherein the aryl or heteroaryl group is optionally substituted at any position, by (one or more) substituents R_{14} or alkyl-R_{14} and the cycloalkyl or heterocycloalkyl group is optionally substituted at any position with (one or more) substituents R_7 or alkyl-R_7, or R_2 is absent;

A is –O-, -O-$(C(R_{15})_2)_n$-, -O-$(C(R_{15})_2)_n$-C(=O)-$(CR_{15})_2)_m$-, -O-$(C(R_{15})_2)_n$-SO_q-$(CR_{15})_2)_m$-, -NR_6-, -NR_6-$(C(R_{15})_2)_n$-, -NR_6-$(C(R_{15})_2)_n$-C(=O)-$(CR_{15})_2)_m$-, -NR_6- $(C(R_{15})_2)_n$-SO_q-$(CR_{15})_2)_m$-, -SO_q-, -SO_q-$(C(R_{15})_2)_n$- or SO_qNR_6;

R_6 is H or alkyl;

n is 1-4;

m is 0-4;

q is 1 or 2;

R_{15} is H or alkyl;

R_7 is carbonyl oxygen (i.e.=O attached to a C atom), CO_2R_8, $CONR_9R_{10}$, $SO_2NR_9R_{10}$, NR_8R_{12}, OR_{11}, alkyl(optionally substituted with one or more halogens), halogen, CN, $NHSO_2CF_3$, tetrazolyl or heterocyclo;

When A is –O-, -O-$(C(R_{15})_2)_n$-, -O-$(C(R_{15})_2)_n$-C(=O)-$(CR_{15})_2)_m$-, -NR_6-, -NR_6-$(C(R_{15})_2)_n$-, -NR_6-$(C(R_{15})_2)_n$-C(=O)-$(CR_{15})_2)_m$-, then

B is heterocyclic ring (substituted at any position with (one or more) substituents R_7 or alkyl-R_7), or alkyl, aryl, heteroaryl(any of which is substituted at any position with (one or more) substituents R_{14} or alkyl-R_{14});

When A is -O-$(C(R_{15})_2)_n$-SO_q-$(CR_{15})2)_m$-, -NR_6- $(C(R_{15})_2)_n$-SO_q-$(CR_{15})_2)_m$-, -SO_q-, -SO_q-$(C(R_{15})_2)_n$- or SO_qNR_6, then;

B is heterocyclic ring (substituted at any position with (one or more) substituents R_7 or alkyl-R_7), or alkyl, aryl, heteroaryl(any of which is substituted at any position with (one or more) substituents R_{14} or alkyl-R_{14});

When R_2 is cycloalkylalkyl, then B is heterocyclic ring (substituted at any position with (one or more) substituents R_7 or alkyl-R_7), or alkyl, aryl, heteroaryl(any of which is substituted at any position with (one or more) substituents R_{14} or alkyl-R_{14}) for all A; and

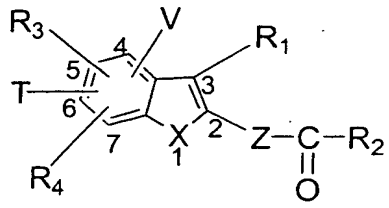
When R_2 is cycloalkylalkyl and A is –O-, B can also be H;

Including N-oxides and pharmaceutically acceptable salts.

3) US 4,933,351 granted patent (Issued on June 12, 1990 to Merck Frosst Canada Inc.,)

Benzofuran 2-carboxy amides useful as inhibitors of leukoriene biosynthesis

One embodiment of the present invention is pharmaceutical composition containing a compound of the formula I and acceptable pharmaceutical carrier:



(I)

wherein :

Z is a bond, $CR_{14}=CR_{15}$;

X is O, S, So or SO_2;

R_2 is H, OH,C_1 toC_{20} alkoxy, including straight chain or branched chain, cycloalkyl, bicycloalkyl, tricycloalkyl or tetracycloalkyl ;

Ar_1-C_1 toC_3 alkoxy;

NR_8Ar_1, wherein R_8 and Ar_1 can optionally be joined to form a heterocyclic ring having 5 to 8 atoms;

-NR_8Het;

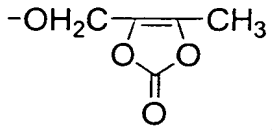
-$N(R_8)CH_2Ar_1$

-$N(R_{13})$-$N(R_{13})_2$ wherein R_{13} is independently hydrogen, R_8, R_9,Ar_1 or Het:

-NH-CH=$C(Ar_1)_2$;

-$O(CH_2)_nNR_8R_9$ wherein N is 2 to 4;

-Z-Ar_1;



;

lower acyloxy-lower alkoxy

(e.g.$OCH(CH_3)OCC(CH_3)_3$);

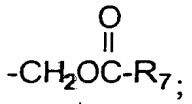
-CH_2OH;

-$(CH_2)_nAr_1$ wherein in n is 0 to 3;

-$(CH_2)_nCOOR_6$ wherein n is 0 to 6;

C_1 toC_{20} alkyl; Ar_1; Het; $(CH_2)_nNR_8R_9$

Wherein n is 1 to 3; or Het;



and R_1, R_3 R_4, T and V are independently selected from

1. hydrogen;
2. alkyl having 1 to 6 carbon atoms;
3. alkenyl having 2 to 6 carbon atoms;
4. $-(CH_2)_nM$ wherein n is 0 to 6 except when X is S and M is oR_5, in which n is 1 to 6 and M is

a) $-OR_5$;

b) halogen;

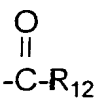
c) $-CF_3$;

d) $-SR_5$;

e) Ar_1;

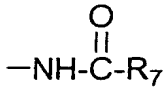
f)$-COOR_6$;

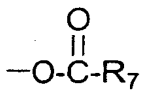
g)

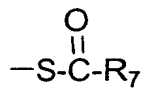


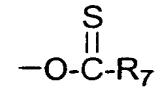
Wherein R_{12} is H , C_1 to C_6 alkyl, or Ar_1;

h) tetrazole;

i) 

j) 

k) 

l) 

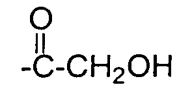
m)

$-NR_8R_{10}$

n)

$-NHSO_2R_{10}$ Wherein R_{10} is OH, C_1 toC_6 alkyl, CF_3, C_1 to C_6 alkoxy, or Ar;

o)



p) $-SOR_5$

q)$-CONR_8R_9$;

r) $-SO_2NR_8R_9$;

s) $-SO_2R_5$;

t) $-NO_2$; or

u) –CN

or any two of R_3,R_4,T and V may be joined to form a saturated ring having 5 to 6 ring atoms, said ring atoms comprising 0,1 or 2atoms selected from oxygen and sulfur, the remaining ring atoms been carbon;

each R_5 is independently H, C_1 to C_6 alkyl, benzene, Ar_1, perfluro-C_1 toC_4 alkyl, CH_2-R_{11} is C_1 toC_5 alkyldimethylamino,hydroxyl-C_2 toC_5 alkyl, CH_2COOR_6, or CH_2CO-R_7;

each R_6 is independently H, or C_1 to C_6 alkyl;

each R_7 is independently C_1 to C_6 alkyl, benzyl,Ar_1,NR_8R_9, $NHAr_1$ or O-C_1 toC_4 alkyl;

each R_8 and R_9 is independently H or C_1 to C_4 alkyl, or R_8 and R_9 may be joined through the N to which they are attached to form a heterocycloalkyl ring having 5 to 8 ring atoms;

each Het is independently an aromatic heterocyclic ring having 5 to 6 ring atoms.one or more of which is selected from N, O and S;

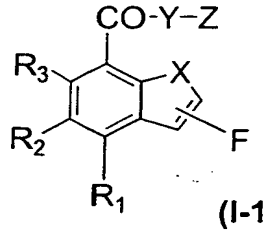
each Ar_1 is independently 1- or 2-naphtyl,phenyl or mono- or disubstituted phenyl, wherein the substituents on phenyl are independently selected from C_1 to C_3 alkyl, I Br. Cl, F, $COOR_6$,$(CH_2)_n$-NR_8R_9 wherein n is 0 to2, methylenedioxy,C_1 to C_3 alkoxy, OH, CN,NO_2; CF_3, C_1 toC_4 acyl, NR_8R_9, S-C_1 to C_6 alkyl, SO-C_1 toC_6 alkyl, and SO_2-C_1 to C_6 alkyl; and

R_{14} and R_{15} are each independently H, C_1 toC_6 alkyl; or a pharmaceutically acceptable salts thereof

4) PCT Patent publication WO 94/08995 (published on April 28, 1994 by Smithkline Beecham Plc)

Heterocyclic condensed benzoic acid derivatives as 5-HT4 receptor antagonists

Compound of formula (I) or a pharmaceutically accepted salts there of:



(I-1)

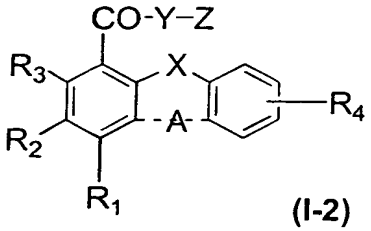
Wherein X is O, or S;

R_1 is hydrogen, amino. halo, C_{1-6} alkyl, hydroxyl or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino, or C_{1-6} alkylthio;

R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or amino;

R_4 is hydrogen or C_{1-6} alkyl;



(I-2)

Wherein

X is O or S

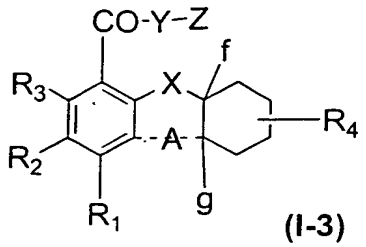
A represent a single bond,-CH_2- or CO or A is $(CH_2)_a$-E-$(CH_2)_b$ where one of a and b is 0 and the other is 0 or 1 and E is O,S or NH;

R_1 is hydrogen, amino. halo, C_{1-6} alkyl, hydroxyl or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino, or C_{1-6} alkylthio;

R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or amino;

R_4 is hydrogen or C_{1-6} alkyl;



(I-3)

Wherein

X is O or S

A represent a single bond,-CH_2- or CO or A is $(CH_2)_a$-E-$(CH_2)_b$ where one of a and b is 0 and the other is 0 or 1 and E is O,S or NH;

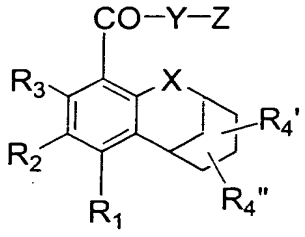
f and g are both hydrogen or together are a bond;

R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxyl or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino, or C_{1-6} alkylthio;

R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or amino;

R_4 is hydrogen or C_{1-6} alkyl;



(I-4)

Wherein

X is O or S;

R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxyl or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino, or C_{1-6} alkylthio;

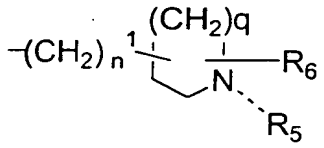
R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or amino;

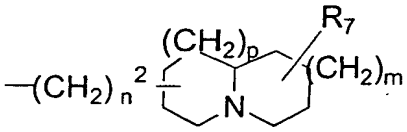
R_4^{I} and R_4^{II} are independently hydrogen or C_{1-6} alkyl;

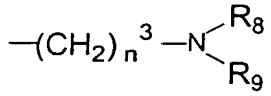
In formulae (I-1) to (I-4) inclusive:

Y is O or NH;

Z is of sub-formula (a), (b) or (c):


(a)


(b)


(C)

Wherein n^1 is 0,1,2,3 or 4; n^2 is 0,1,2,3 or 4; n^3 is 2,3,4 or 5;

q is 0,1,2 or 3; p is 0,1 or 2; m is 0,1 or 2;

R_5 is hydrogen, C_{1-12} alkyl, aralkyl or R_5 is $(CH_2)_z$-R_{10} wherein z is 2 or3 and R_{10} is selected from cyano, hydroxyl, C_{1-6} alkoxy, phenoxy, $C(O)C_{1-6}$ alkyl, COC_6H_5, -$CONR_{11}R_{12}$, $NR_{11}COR_{12}$, $SO_2NR_{11}R_{12}$ or $NR_{11}SO_2R_{12}$, wherein R_{11} and R_{12} are hydrogen or C_{1-6} alkyl; and

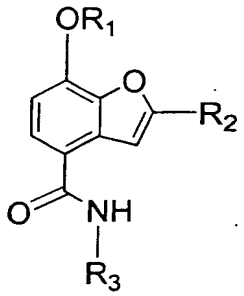
R_6, R_7 and R_8 are independently hydrogen or C_{1-6} alkyl; and

R_9 is hydrogen or C_{1-10} alkyl;

or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere;

5) PCT Patent publication WO 01/58895-A1 (published on August 16, 2001 by Darwin Discovery Limited)

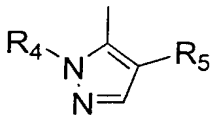
This invention provides novel compounds having therapeutic utility, in particular for the treatment of disease states associated with proteins which mediate cellular activity, for example by inhibiting TNF and / or PDE-IV. According to the invention, the compounds of formula (i):



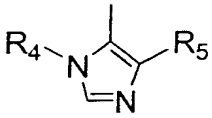
wherein R_1 is C_{1-3} alkyl optionally substituted with one or more fluorines;

R_2 is CH_2OCH_3 or 2 or 3–tetrahydrofuranyl;

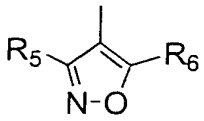
R_3 is a pyrazole, imidazole or isoxazole group of a partial formula (A), (B) or (C)



(A)



(B)



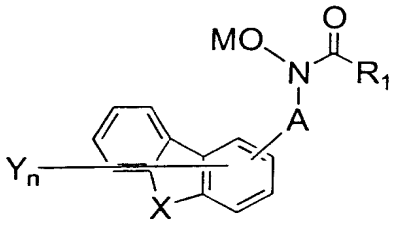
(C)

R_4 is C_{1-3} alkyl; and

R_5 and R_6, which may be same or different, each represents C_{1-3} alkyl, halogen, CF_3 or CN;

6) US granted patent 4,769, 387 (Issued on September 06, 1988 to Abbott Laboratories)

In accordance with the present invention, there are 5-and / or 12-lipoxygenase inhibiting compounds of the formula:



wherein R is (1) hydrogen, (2) C_1 to C_4 alkyl, (3) C_2 to C_4 alkenyl, or (4) NR_2R_3, wherein R_2 and R_3 are independently selected from hydrogen, C_1 to C_4 alkyl or hydroxyl, but R_2 and R_3 are not simultaneously hydroxyl;

X (1) oxygen, (2) sulfur, (3) SO_2, or (4) NR_4 wherein R_4 is (1) hydrogen, (2) C_1 toC_6 alkyl, (3) C_1 to C_6 alkoyl, or (4) aroyl;

A is selected from C_1 to C_6 alkylene and C_2 to C_6 alkenylene;

Y is selected independently at each occurrence from (1) hydrogen, (2) halogen, (3) hydroxy, (4) cyano (5) halosubstituted alkyl, (6) C_1 to C_{12} alkyl, (7) C_2 to C_{12} alkenyl, (8) C_1 to C_{12} alkoxy, (9) C_3 to C_8 cycloalkyl, (10) aryl, (11) aryloxy, (12) aroyl, (13) C_1 to C_{12} arylalkyl, (14) C_2 to C_{12} arylalkenyl, (15) C_1 to C_{12} arylalkoxy, (16) C_1 to C_{12} arylthioalkoxy, and substituted derivatives of (17) aryl, (18) aryl-oxy, (19) aroyl, (20) C_1 to

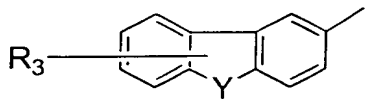
C_{12} arylalkyl, (21) C_2 to C_{12} arylalkenyl, (22) C_1 toC_{12} arylalkoxy, or (23) C_1 to C_{12} arylthioalkoxy, wherein substituents are selected from halo, nitro, cyano C_1 toC_{12} alkyl, alkoxy, and halosubstituted alkyl; the number n is 0–4; the group(s) Y may be substituted from any of the positions on the aryl rings;
and M is hydrogen, a pharmaceutically acceptable cation, aroyl, or C_1 to C_{12} alkoyl.

7) US granted patent US 3, 897,453 (Issued on July 29, 1975 to Merck Patent Gesellschaft mitbeschrankter Haftung)

The novel compounds of the invention are dibenzofuran and dibenzothiophene derivatives of the general formula I

$$Z\text{-}CHR_1R_2 \qquad (I)$$

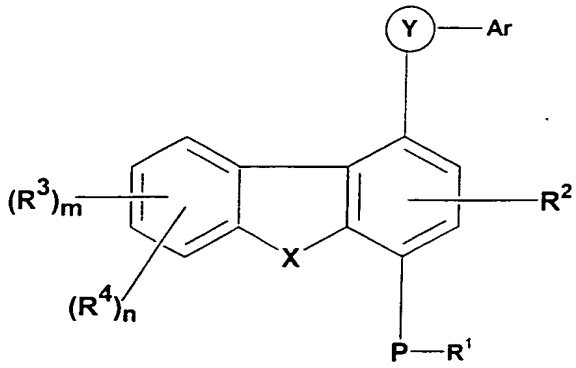
In which Z is



wherein R_1 is COOH, CHO, or CH_2OH including functional derivatives thereof; R_2 is H or alkyl of 1-4 carbon atoms; R_3 is H, alkyl, alkoxy, alkanoyl, monoalkylamino, dialkylamino, or acylamino, each of up to 4 carbon atoms, F, Cl, Br, I, OH, NH_2, NO_2, CN, or CF_3; and Y is O or S; with the proviso that at least one of R_2 and R_3 is other than H; and the physiologically acceptable salts thereof.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides novel heterocyclic compounds of the general formula



(1)

wherein:

R^1, R^2 and R^3 may be same or different and are independently selected from the groups consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, protecting groups, –C(O)-R^a, -C(O)O-R^a, -C(O)NR^aR^a , -$S(O)_q$-R^a, -$S(O)_q$-NR^aR^a , -NR^aR^a, ,-OR^a, -SR^a or when two R^3 substitutents ortho to each other, may be joined to a form a saturated or unsaturated ring, which may optionally include up to two heteroatoms which may be same or different selected from O, NR^L or S;

wherein R^4 represents -NR^5R^6 or -C(=L)-R^5; in which R^5 and R^6 may be same or different and are independently selected from the groups consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl,

substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl, nitro, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^a$, $-S(O)_q-R^a$, $-S(O)_q-NR^aR^a$, $-C(=NR^a)-R^a$, $-C(=NR^a)-NR^aR^a$, $-C(=S)-NR^aR^a$, $-C(=S)-R^a$, $-N=C(R^aR^a)$, $-NR^aR^a$, $-OR^a$, $-SR^a$, protecting groups or R^5 and R^6 to each other may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms which may be same or different selected from O, NR^a or S;

Ar is substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclic ring or substituted or unsubstituted heteroaryl ring;

Preferably Ar is optionally substituted phenyl, optionally substituted pyridyl or optionally substituted pyridyl-N-oxide in which optional substituents (one ore more) may be same or different and are independently selected from the groups consisting of hydrogen, hydroxyl, halogen, cyano, nitro, carboxyl, trifluoroalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted amino or mono or di substituted or unsubstituted alkylamino

X is O, $S(O)_q$ or NR^a;

Y is $-C(O)NR^7$, $-NR^7S(O)_q$, $-S(O)_qNR^7$ or $-NR^7C(O)$; Wherein q is 0, 1 or 2;

R^7 is hydrogen, substituted or unsubstituted alkyl, hydroxyl, $-OR^a$, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic ring ;

wherein P represents O , S;

wherein m represents 0 – 3;

wherein n represents 1 – 4;

wherein L represents O, S or NR^a;

wherein q represents 0,1 or 2

Wherein R^a represents hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, protecting groups, –C(O)-R^a, -C(O)O-R^a, -C(O)NR^aR^a , -$S(O)_q$-R^a, -$S(O)_q$-NR^aR^a , -NR^aR^a, -OR^a or -SR^a;

with the provisos;

1) when R^5 is a hydrogen, the R^6 is not hydrogen;

2) when R^6 is a hydrogen, the R^5 is not hydrogen;

The present invention also relates to a process for the preparation of the above said novel heterocyclic compounds of the formula **(1)** as defined above. The compounds of general formula **(1)** more particularly, down regulate or inhibit the production of TNF-α as they are PDE4 inhibitors and therefore are useful in the treatment of variety of allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjuctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, diabetes, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. The compounds of the present invention are particularly useful for the treatment of asthma and chronic obstructive pulmonary disease (COPD)

DETAILED DESCRIPTION OF THE INVENTION

The term 'alkyl' refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl), and the like .

The term "Alkenyl " refers to aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched or branched chain having about 2 to

about 10 carbon atoms in the e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

The term " Alkynyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 10 carbon atoms presently being preferred) e.g., ethynyl, propynyl, butnyl and the like.

The term "Alkoxy" denotes alkyl group as defined above attached via oxygen linkage to the rest of the molecule. Representative examples of those groups are $-OCH_3$, $-OC_2H_5$ and the like

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of about 3 to 12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and examples of multicycic cycloalkyl groups include perhydronaphthyl, adamantyl and norbornyl groups bridged cyclic group or sprirobicyclic groups e.g sprio (4,4) non-2-yl.

The term " cycloalkylalkyl" refers to cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms directly attached to alkyl group which then attached to the main structure at any carbon from alkyl group that results in the creation of a stable structure. such as cyclopropylmethyl, cyclobuylethyl, cyclopentylethyl, and the like.

The term " cycloalkenyl" refers to cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms with atleast one carbon- carbon double bond such as cyclopropenyl, cyclobutenyl, cyclopentenyl and the like.

The term "aryl" refers to aromatic radicals having in the range of 6 up to 14 carbon atoms such as phenyl, naphthyl, tetrahydronapthyl, indanyl, biphenyl and the like.

The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above. e.g., $-CH_2C_6H_5$, $-C_2H_5C_6H_5$ and the like.

The term "Heterocyclic ring" refers to a stable 3- to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purpose of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen

or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofurnyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl, tetrahydroisouinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxasolidinyl, triazolyl, indanyl, isoxazolyl, isoxasolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofurtyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide thiamorpholinyl sulfone, dioxaphospholanyl , oxadiazolyl , chromanyl, isochromanyl and the like.

The term "Heteroaryl" refers to heterocyclic ring radical as defined above. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "Heteroarylalkyl" refers to heteroaryl ring radical as defined above directly bonded to alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from alkyl group that results in the creation of a stable structure.

The term "Heterocyclyl" refers to a heterocylic ring radical as defined above. The heterocylyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "Heterocyclylalkyl" refers to a heterocylic ring radical as defined above directly bonded to alkyl group. The heterocyclylalkyl radical may be attached to the main structure at carbon atom in the alkyl group that results in the creation of a stable structure.

The term "cyclic ring " refers to a cyclic group containing 3-10 carbon atoms

The term "protecting group" refers to CBZ or BOC and the like

The term "Halogen" refers to radicals of Fluorine, Chlorine, Bromine, Iodine

The substituents in the 'substituted alkyl', 'substituted alkoxy' 'substituted alkenyl' ' substituted alkynyl' 'substituted cycloalkyl' substituted cycloalkylalkyl' substituted cyclocalkenyl' 'substituted arylalkyl' 'substituted aryl' 'substituted heterocyclic ring', 'substituted heteroaryl ring,' 'substituted heteroarylalkyl', 'substituted heterocyclylalkyl ring', 'substituted amino', 'substituted alkoxycarbonyl' 'substituted alkylcarbonyl', 'substituted alkylcarbonyloxy' and 'substituted carboxylic acid' may be the same or different which one or more selected from the groups such as hydrogen, hydroxy, halogen, carboxyl, cyano, amino, nitro, oxo (=O), thio (=S), formyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, aryl, heteroaryl, heterocyclic ring, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-N(R^x)CO-$, $-(=N-N(R^x)R^y)$, $-N(R^x)R^yCO-$, $-NR^xR^yC(O)OR^z$, $-NR^xR^y$, $-NR^xC(O)R^y-$, $-NR^xC(S)R^y$ - $NR^xC(S)NR^yR^z$, $-N(R^x)SO-$, $-NR^xSO_2-$, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y-$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yR^z$, $-R^xR^yR^z$, $-R^xCF_3$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xCS$. $-R^xC(O)R^x$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, or $-ONO_2$,(wherein R^x, R^y and R^z in each of the above groups can be hydrogen atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstitued heterocyclic ring, substituted or unsubstitued heterocyclylalkyl, substituted or unsubstitued heteroaryl or substituted or unsubstitued heteroarylalkyl.

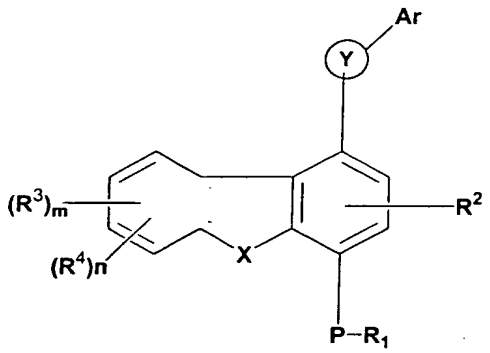
Pharmaceutically acceptable salts forming part of this invention include salts derived from inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, Mn; salts of organic bases such as N,N'-diacetylethylenediamine, glucamine, triethylamine, choline, choline hydroxide, dicyclohexylamine, metformin, benzylamine, trialkylamine, thiamine, spermidine, and the like; chiral bases like alkylphenylamine, glycinol, phenyl glycinol and the like, salts of natural amino acids such as glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, omithine, lysine, arginine, serine, and the like; unnatural amino acids such as D-isomers or substituted amino acids; guanidine, substituted guanidine wherein the substituents are selected from nitro,

amino, alkyl, alkenyl, alkynyl, ammonium or substituted ammonium salts and aluminum salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, benzoates, salicylates, , benzenesulfonates. ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprise other solvents of crystallization such as alcohols.

Some of the representative compounds according to the present invention are specified below but should not construed to be limited thereto;

The compounds according to the invention may be prepared by the following processes. The symbols P, Ar, X, Y, R^1, R^2, R^3, R^4, m and n when used in the below formulae below are to be understood to present those groups described above in relation to formula **(1)** unless otherwise indicated

The present invention discloses a process for the preparation of compounds of general formula **(1).**



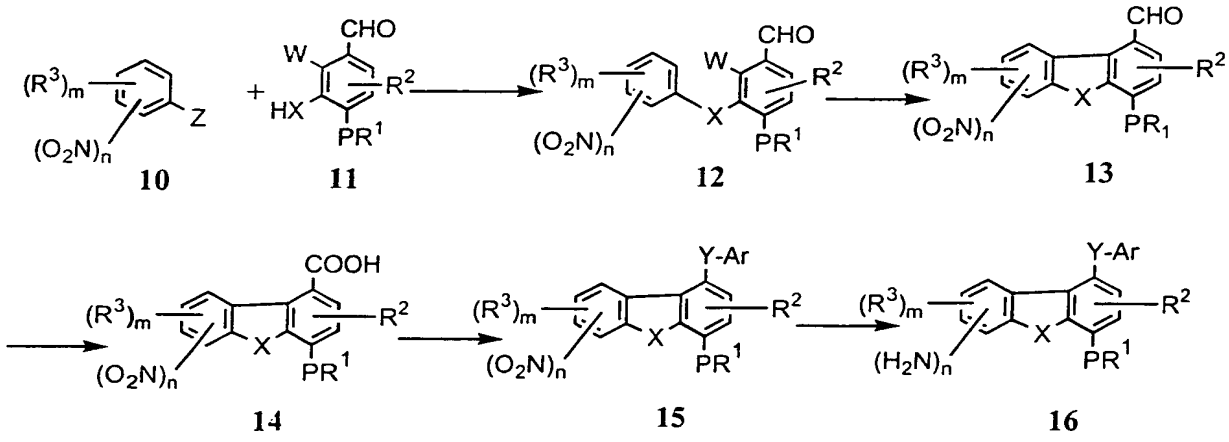
(1)

In one embodiment, the desired compounds of the formula **(1)** wherein Y is –$CONR^7$; R^4 is $-NR^5R^6$; P, Ar, X, Y, R^1, R^2, R^3, R^5, R^6 , R^7, m and n are as described in the general description, can be synthesized from a common intermediate of the formula **(16)**.

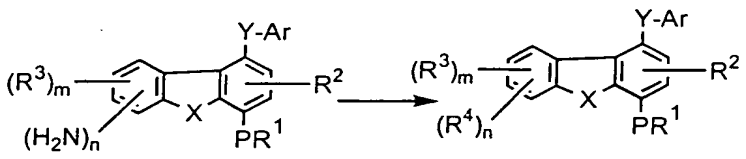
The common intermediate of the formula **(16)** can be synthesized by using the general process described in synthetic scheme **I**. In this an optionally substituted halonitrobenzene of the formula **(10)** wherein Z is a halogen, preferably a fluorine, is

reacted with an optionally substituted benzaldehyde of the general formula **(11)** wherein W is a halogen, preferably bromine or iodine, under basic conditions to obtain the intermediate of the general formula **(12)**. The intermediate of the general formula **(12)** can be cyclised using metal compound or metal catalysed coupling conditions, preferably palladium acetate, to the tricyclic intermediate **(13)**. The tricyclic intermediate of the general formula **(13)** is the oxidized to the carboxylic acid of the general formula **(14)** using standard formyl oxidation processes known in the literature. The intermediate of the general formula **(14)** is then converted to the intermediate of the general formula **(15)**, wherein Y is $-CONR^7$, by reacting the appropriately activated carboxylic acid (acid halide or mixed anhydride) intermediate of the general formula **(14)** with the optionally substituted aryl or heteroaryl amines ($ArNHR^7$) under appropriate basic conditions reported in the literature. The intermediate of the general formula **(15)** is the reduced using conventional methods known in the literature to the amino intermediate of the general formula **(16)**.

SYNTHETIC SCHEME I.



The intermediate of the of the general formula **(16)** can be converted as follows to the desired compounds of the general formula **(1)** wherein Y is $-CONR^7$, R^4 is $-NR^5R^6$; P, Ar, X, Y, R^1, R^2, R^3, R^5, R^6 ,R^7, m and n are as described in the general description, using conventional methods known in the literature.



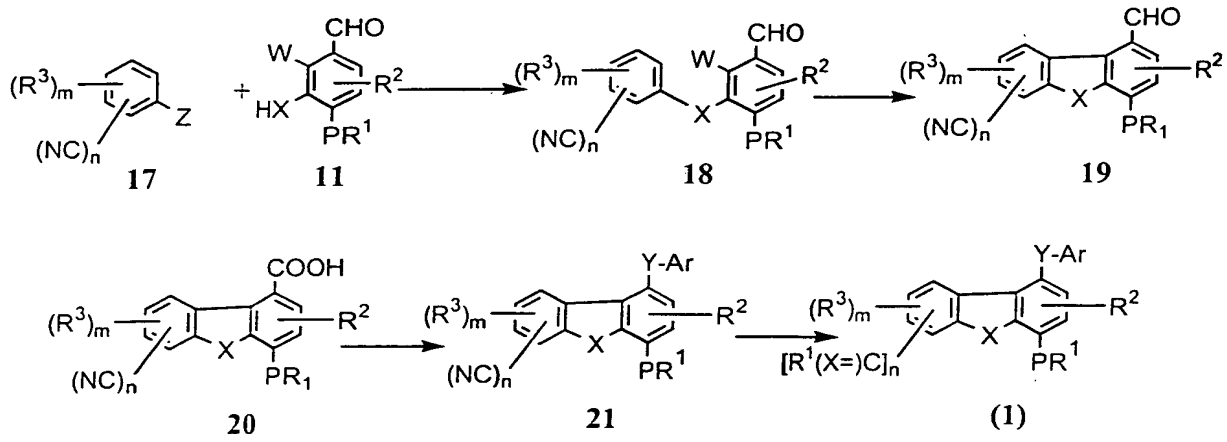
16 (1)

The desired compounds of the formula **(1)** obtained are then converted into their salts and/or the N-oxides and, if desired, salts of the compounds of the formula **(1)** obtained are then converted into the free compounds.

In yet another embodiment, the desired compounds of the general formula **(1)** wherein Y is $-CONR^7$; R^4 is $-C(=L)-R^5$; P, Ar, X, Y, R^1, R^2, R^3, R^5, m and n are as described in the general description, can be synthesized from a common intermediate of the general formula **(21)**.

The common intermediate of the general formula **(21)** can be synthesized by using the general process described in synthetic scheme **II**. In this an optionally substituted halocyanobenzene of the general formula **(17)** wherein Z is a halogen, preferably a fluorine, is reacted with an optionally substituted benzaldehyde of the general formula **(11)** wherein W is a halogen, preferably bromine or iodine, under basic conditions to obtain the intermediate of the genral formula **(18)**. The intermediate of the general formula **(18)** can be cyclised using metal compound or metal catalysed coupling conditions, preferably palladium acetate, to the tricyclic intermediate **(19)**. The tricyclic intermediate of the general formula **(19)** is the oxidized to the carboxylic acid of the general formula **(20)** using standard formyl oxidation processes known in the literature. The intermediate of the general formula **(20)** is then converted to the cyano intermediate of the general formula **(21)** where Y is $-CONR^7$, by reacting the appropriately activated carboxylic acid (acid halide or mixed anhydride) intermediate **(20)** with the optionally substituted aryl or heteroaryl amines ($ArNHR^7$) under appropriate basic conditions reported in the literature. This common intermediate of the general formula **(21)** can be converted to the desired compounds of the formula **(1)** wherein Y is $-CONR^7$, R^4 is $-C(=X)-R^5$; P, Ar, X, Y, R^1, R^2, R^3, R^5, m and n are as described in the general description, using conventional methods known in the literature.

SYNTHETIC SCHEME II.



The desired compounds of the formula **(1)** wherein Y is $-CONR^7$, R^4 is $-C(=X)-R^5$; P, Ar, X, Y, R^1, R^2, R^3, R^5, m and n are as described in the general description obtained are then converted into their salts and/or the N-oxides and, if desired, salts of the compounds of the formula (1) obtained are then converted into the free compounds.

The N-oxidation is carried out in a manner likewise familiar to the person skilled in the art, e.g with the aid of m-chloroperoxybenzoic acid in dichloromethane at room temperature. The person skilled in the art is familiar with the reaction conditions which are necessary for carrying out the process on the basis of his expert knowledge.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuum and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent, e.g in a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol (ethanol, isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecepiting, precipitating with a non-solvent for the addition salt or by evaporating the

solvent. Salts obtained can be converted by basification or by acidifying into the free compounds which, in turn can be converted into salts.

In general, the ethereal solvents used in the above described processes for the preparation of compounds of the formula (1) are selected from diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran, diisopropyl ether, 1,4 dioxane and the like. The chlorinated solvent which may be employed may be selected from dichloromethane, 1,2-dichloroethane, chloroform, carbontetrachloride and the like . The aromatic solvents which may be employed may be selected from benzene, toluene. The alchoholic solvents which may be employed may be selected from methanol, ethanol, n-propanol, iso propanol, tert.butanol and the like. The aprotic solvents which may be employed may be selected from N, N-dimethylformamide, dimethyl sulfoxide and the like.

In general, the compounds prepared in the above described processes are obtained in pure form by using well known techniques such as crystallization using solvents such as pentane, diethyl ether, isopropyl ether, chloroform, dichloromethane, ethyl acetate, acetone, methanol, ethanol, iso propanol, water or their combinations, or column chromatography using Alumina or silica gel and eluting the column with solvents such as hexane, petroleum ether (pet.ether), chloroform, ethyl acetate, acetone, methanol or their combinations.

Various polymorphs of a compound of general formula **(1)** forming part of this invention may be prepared by crystallization of compound of formula **(1)** under different conditions. example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures, various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The present invention also provides pharmaceutical compositions, containing compounds of the general formula **(1)** as defined above, their derivatives, their analogs, their

tautomeric forms, their stereoisomers, their polymorphs, their enantiomers, their diasteromers, their pharmaceutically acceptable salts or their pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like. The pharmaceutical compositions according to this invention can be used for the treatment of allergic disorders.

It will be appreciated that some of the compounds of the general formula **(1)** defined above according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centers in the compounds of the general formula **(1)** can give rise to stereoisomers and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers and their mixtures, including racemic mixtures.

The invention may also contain E & Z geometrical isomers wherever possible in the compounds of the general formula **(1)** which includes the single isomer or mixture of both the isomers

The pharmaceutical compositions may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like and may contain flavorants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. The active compounds of the formula **(1)** will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in the range as described above. Thus, for oral administration, the compounds of the formula **(1)** can be combined with a suitable solid, liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parenteral administration, the compounds of the formula **(1)** can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds

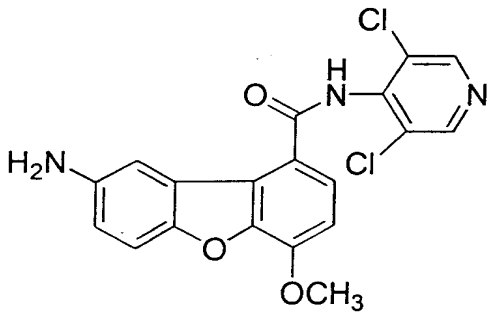
of the formula (**1**). The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

In addition to the compounds of formula (**1**) the pharmaceutical compositions of the present invention may also contain or be co-administered with one or more known drugs selected from other clinically useful therapeutic agents.

The invention is explained in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

Intermediate 1

N-(3,5-dichloropyrid-4-yl)-4-methoxy-8-amino dibenzo[b,d]furan-1-carboxamide



Step 1: 2-Bromoisovanillin

Isovanillin (5 gm, 0.033 mol) was dissolved in glacial acetic acid (30 ml). Anhydrous sodium acetate (5.4 gm) was added to the above solution followed by powdered iron (0.15 gm). The system was flushed thoroughly with nitrogen. A solution of bromine (5.79 gm, 0.0362 mol) in glacial acetic acid (10 ml) was added to the above stirred suspension at 105°C over a period of 15 min. The reaction mixture was cooled and stirred at room temperature for 45 min. The reaction mixture was poured into aqueous 2% sodium bisulfite (200 ml) and stirred for 10 min. The precipitate was filtered washed with water (100 ml), and dried to obtain 3.5 gm of 2-bromoisovanillin as white powder mp: (200-202°C).

IR (KBr) 3233, 2990, 2891, 2844, 1669, 1593, 1564, 1494, 1463, 1286, 1238, 1205, 1019, 987, 805, 786 cm^{-1}.

^1H nmr (300 MHz, $CDCl_3$) δ 3.99 (s, 3H), 6.13 (s, 1H), 6.89 (d, 1H, J = 8.4 Hz), 7.55 (d, 1H, J = 8.4 Hz), 10.23 (s, 1H).

Step 2: 2-Bromo-3-(p-nitrophenoxy)-4-methoxy benzaldehyde

To a stirred suspension of potassium fluoride (1.89 gm, 0.0326 mol) in dry DMSO (10 ml) was added a solution of 2-bromoisovanillin (5.0 gm, 0.0217 mol) in DMSO (10 ml). A solution of 4-fluoronitrobenzene (5.0 gm, 0.0260 mol) in DMSO (5 ml) was added to the above suspension and the reaction mixture was stirred at 140°C for 4 h. The reaction mixture was cooled to room temperature and the contents were poured into water (150 ml) and extracted with ethyl acetate (50 ml x 3). The organic extracts were combined and washed with 1N sodium hydroxide (25 ml x 2), water and brine and dried over anhydrous sodium sulfate. The dried organic layer was concentrated in vacuo and the residue was purified by silica-gel column chromatography using 20% ethyl acetate-petroleum ether as the eluent to give 2-bromo-3-(p-nitrophenoxy)-4-methoxy benzaldehyde as a pale yellow solid (5.0 gm) mp:132-140°C.

IR (KBr) 3084, 2874, 1689, 1584, 1506, 1486, 1348, 1285, 1253, 1234, 1114, 1025, 848, 815, 747 cm^{-1}.

^1H nmr (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.89 (d, 2H, J = 7.2 Hz), 7.07 (d, 1H, J = 9.0 Hz), 7.92 (d, 1H, J = 8.4 Hz), 8.17 (d, 2H, J = 9.0 Hz), 10.24 (s, 1H).

Step 3: 4-methoxy-8-nitro-1-formyl dibenzo[b,d]furan

2-Bromo-3-(p-nitrophenoxy)-4-methoxy benzaldehyde (3.5 gm, 0.0087 mol), anhydrous sodium carbonate (1.125 gm, 0.0106 mol) and palladium (II) acetate (0.19 gm, 0.0008 mol), in dimethylacetamide (15 ml) are heated and stirred under nitrogen at 170°C for 2h. Water (90 ml) is added to the cooled reaction mixture. The precipitated solid is collected by filteration and washed with 5% hydrochloric acid followed by water. The product was obtained as a yellow solid (3.4 gm).

IR (KBr) 3115, 2925, 2856, 1682, 1609, 1576, 1522, 1343, 1295, 1076, 846, 829 cm^{-1}.

^1H nmr (300 MHz, DMSO) δ 4.13 (s, 3H), 7.53 (d, 1 H, J = 9.0 Hz), 8.01 (d, 1H, J = 9.0 Hz), 8.16 (d, 1H, J = 9.0 Hz), 8.48 (dd, 1H, J = 9.0 Hz, 3.0 Hz), 9.79 (d, 1H, J = 3.0 Hz), 10.1 (s, 1H).

Step 4: 4-methoxy-8-nitro dibenzo[b,d]furan-1-carboxylic acid

4-methoxy-8-nitro-1-formyl dibenzo[b,d]furan (1.1 gm, 0.0034 mol) in acetone (5 ml) was heated to 60-70°C for 10 min. To the above suspension was added dropwise a hot solution of potassium permanganate (1.07 gm, 0.0068 mol) in water: acetone (1: 3) (15 ml) for 10 min. The reaction was heated to 60-70oC for 10 min., cooled to room temperature and filtered. The residue washed with acetone and the filterate was extracted with 10% sodium hydroxide solution. Acidification, followed by filteration and washing of the precipitate yielded 4-methoxy-8-nitro-dibenzo[b,d]furan-1-carboxylic acid (0.6 gm) as white solid; mp: 178°C (dec.)

IR (KBr) 3467, 2942, 1711, 1694, 1633, 1610, 1574, 1522, 1453, 1417, 1344, 1278, 1069, 846, 826, 743 cm^{-1}.

^1H nmr (300 MHz, DMSO) δ 4.08 (s, 3H), 7.36 (d, 1 H, J = 8.4 Hz), 7.98 (d, 1H, J = 9.0 Hz), 8.07 (d, 1H, J = 8.4 Hz), 8.44 (dd, 1H, J = 9.0 Hz, 2.7 Hz), 9.79 (d, 1H, J = 2.4 Hz),

Step 5a : 4-methoxy-8-nitro dibenzo[b,d]furan-1-carboxylic acid chloride

was synthesized from 4-methoxy-8-nitro dibenzo[b,d]furan-1-carboxylic acid using reaction conditions described in step 5a of example 1.

Step 5b: N-(3,5-dichloropyrid-4-yl) - 4-methoxy-8-nitro dibenzo[b,d]furan-1-carboxamide

To a pre-washed suspension of sodium hydride (52 mg, 2.5 equiv., 1.3 mmol, 60% oil dispersion) in DMF (2 ml) was added drop wise a solution of 4-amino-3,5-dichloropyridine (93 mg, 0.52 mmol) in DMF (2 ml) at –10°C. A pre-cooled solution of above acid chloride (0.52 mmol) (from step 5a) in THF (2 ml) was added, all at once, to the reaction mixture

and the contents were stirred at −10°C for 30 min. The reaction was quenched with brine, diluted with water and filtered to give a crude solid which was washed with ethanol to give N-(3, 5-dichloropyrid-4-yl)-4-methoxy-8-nitro-dibenzo[b,d]furan-1-carboxamide as a white solid (80 mg); mp: 315-317 °C.

IR (KBr): 3245, 3092, 2845, 1662, 1614, 1581, 1554, 1519, 1483, 1461, 1439, 1391, 1337, 1282, 1205, 1181, 1067 cm-1.

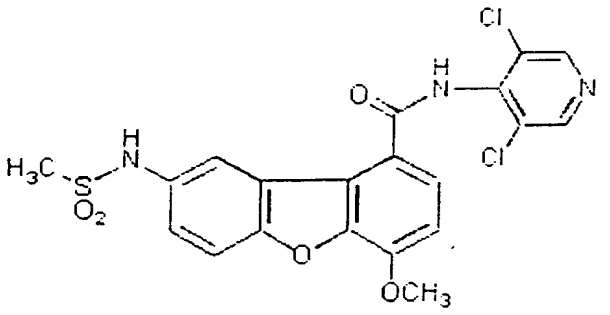
^{1}H nmr (300 MHz, DMSO) δ 4.12 (s, 3H), 7.48 (d, 1 H, J = 8.1 Hz), 8.03 (d, 1H, J = 8.1 Hz), 8.06 (d, 1H, J = 8.4 Hz), 8.44 (dd, 1H, J = 7.2 Hz), 8.81 (s, 2H). 9.43 (d, 1H, J = 1.2 Hz), 10.95 (s, 1H).

Step 6: N-(3,5-dichloropyrid-4-yl) - 4-methoxy-8-amino-dibenzo[b,d]furan-1-carboxamide

Iron powder (467 mg, 8.35 mmol) and ammonium chloride (742 mg, 13.5 mmol) were heated at 80oC for 15 min. N-(pyrid-4-yl)-4-methoxy-8-nitro dibenzo[b,d]furan-1-carboxamide (800 mg, 1.85 mmol) was suspended in methanol and allowed to trickle down into the above reaction mixture at reflux. The reaction was refluxed for 3 h and filtered hot. Methanol was evaporated, and the solid was washed with water and taken directly without purification to synthesize the following examples.

Example 1

N-(3,5-dichloropyrid-4-yl)-4-methoxy-8-methanesulfonamido-dibenzo[b,d]furan-1-carboxamide



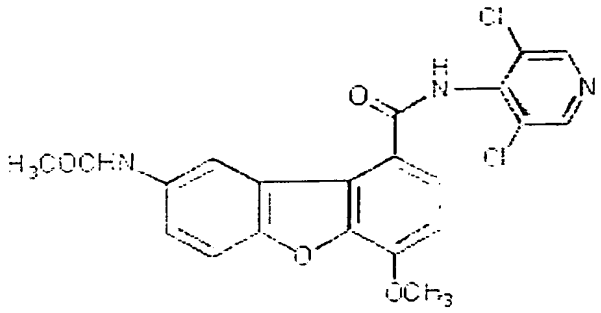
N-(3,5-dichloropyrid-4-yl) - 4-methoxy-8-amino-dibenzo[b,d]furan-1-carboxamide (100 mg, 0.249 mmol) (intermediate 1) was treated with methanesulfonyl chloride (24 mg, 0.299 mol) in THF (10 ml) containing pyridine (23 mg, 0.299 mmol) at 0oC and allowed to warm to room temperature. The reaction was stirred at room temperature for 30 min. THF was evaporated and the residue was washed with saturated sodium bicarbonate solution, water. The solid obtained was purified by silica gel column chromatography using 30 % acetone-chloroform as eluent to obtain 30 mg of N-(3,5-dichloropyrid-4-yl) - 4-methoxy-8-methanesulfonylamido-dibenzo[b,d]furan-1-carboxamide as white solid; mp: 315°C.

IR (KBr): 3272, 3147, 2925, 1661, 1607, 1490, 1393, 1313, 1288, 1145, 1101, 810 cm-1.

^{1}H nmr (300 MHz, DMSO) δ 2.91 (s, 3H), 4.07 (s, 3H), 7.35 (d, 1H, J = 8.4 Hz), 7.44 (d, 1H, J = 8.4 Hz), 7.73 (d, 1H, J = 8.4 Hz), 7.80 (d, 1H, J = 8.4 Hz), 8.31 (s, 1H), 8.77 (s, 1H), 9.65 (s, 1H), 10.80 (s, 1H).

Example 2

N-(3,5-dichloropyrid-4-yl)-4-methoxy-8-acetamido-dibenzo[b,d]furan-1-carboxamide



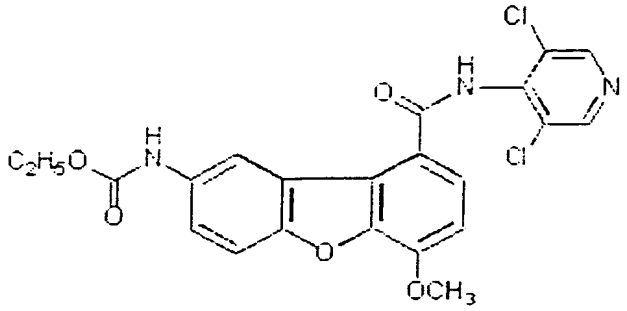
N-(3,5-dichloropyrid-4-yl) - 4-methoxy-8-amino-dibenzo[b,d]furan-1-carboxamide (100 mg, 0.249 mmol) (intermediate 1) was treated with acetyl chloride (22 mg, 0.299 mmol) in THF (10 ml) containing pyridine (23 mg, 0.299 mmol) at 0oC and allowed to warm to room temperature. The reaction was stirred at room temperature for 30 min. THF was evaporated and the residue was washed with saturated sodium bicarbonate solution and water. The solid obtained was purified by silica gel column chromatography using 30 % acetone-chloroform as eluent to obtain 25 mg of N-(3,5-dichloropyrid-4-yl) - 4-methoxy-8-acetamido-dibenzo[b,d]furan-1-carboxamide as white solid; mp: 252°C.

IR (KBr): 3271, 2961, 2925, 2852, 1660, 1607, 1542, 1499, 1468, 1392, 1285, 1261, 1101, 1021, 805 cm^{-1}.

^1H nmr (300 MHz, DMSO) δ 2.01 (s, 3H), 4.07 (s, 3H), 7.32 (d, 1H, J = 8.4 Hz), 7.65 (d, 1H, J = 8.4 Hz), 7.93 (m, 2H), 8.41 (s, 1H), 8.76 (s, 2H), 10.06 (s, 1H), 10.76 (s, 1H).

Example 3

N-(3,5-dichloropyrid-4-yl)-4-methoxy-8-ethoxycarboxamido-dibenzo[b,d]furan-1-carboxamide



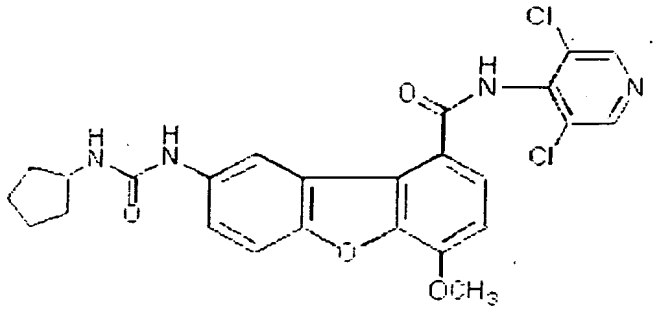
N-(3,5-dichloropyrid-4-yl) - 4-methoxy-8-amino-dibenzo[b,d]furan-1-carboxamide (100 mg, 0.249 mmol) (intermediate 1) was treated with ethyl chloroformate (40 mg, 0.374 mmol) in THF (10 ml) containing pyridine (29 mg, 0.374 mmol) at 0oC and allowed to warm to room temperature. The reaction was stirred at room temperature for 30 min. THF was evaporated and the residue was washed with water. The solid obtained was purified by silica gel column chromatography using 10 % acetone-chloroform as eluent to obtain 40 mg of N-(3,5-dichloropyrid-4-yl) - 4-methoxy-8-ethoxycarboxamido-dibenzo[b,d]furan-1-carboxamide as white solid; mp: 274°C.

IR (KBr): 3244, 3074, 2970, 2928, 1733, 1674, 1600, 1578, 1550, 1479, 1391, 1278, 1236, 1210, 1102, 1062, 803 cm^{-1}.

^1H nmr (300 MHz, DMSO) δ 1.24 (t, 3H), 4.07 (s, 3H), 4.08 (q, 2H), 7.32 (d, 1H, J = 8.1 Hz), 7.60-7.67 (d, 2H), 7.88 (d, 1H, J = 8.1 Hz), 8.45 (s, 1H), 8.76 (s, 2H), 9.62 (s, 1H), 10. 76 (s, 1H).

Example 4

N-(3,5-dichloropyrid-4-yl)-4-methoxy-8-cyclopentylaminocarboxamido-dibenzo[b,d]furan-1-carboxamide



A solution of cyclopentylamine (21 mg, 0.273 mmol) in THF (3 ml) was cooled to -30oC. To this solution was added triethylamine (37 mg, 0.374 mmol) and stirred for 10 min. A solution of triphosgene (73 mg, 0.249 mmol) in THF (3 ml) was added at -30oC to the above solution and stirred for 30 min at room temperature. This solution was then added to a suspension of N-(3,5-dichloropyrid-4-yl) - 4-methoxy-8-amino-dibenzo[b,d]furan-1-carboxamide (100 mg, 0.249 mmol) (intermediate 1) and pyridine (29 mg, 0.374 mmol) in THF (5 ml). The reaction was stirred at room temperature for 30 min. THF was evaporated and the residue was washed with water. The solid obtained was purified by silica gel column chromatography using 10 % acetone-chloroform as eluent to obtain 15 mg of N-(3,5-dichloropyrid-4-yl) - 4-methoxy-8-cyclopentylamino carboxamido-dibenzo[b,d]furan-1-carboxamide as white solid; mp: >268°C (dec) .

IR (KBr): 3326, 2956, 2869, 1687, 1630, 1607, 1552, 1478, 1389, 1279, 1198, 1102, 1021, 809 cm^{-1}.

^1H nmr (300 MHz, DMSO) δ 1.3-1.5 (m, 4H), 1.5-1.7 (m, 4H), 4.07 (s, 3H), 5.60 (brm, 1H), 7.32 (d, 1H, J = 8.1 Hz), 7.66 (brm, 1H), 7.90 (d, 1H, J = 1.8 Hz), 8.38 (s, 1H), 8.74 (s, 2H), 9.73 (s, 1H), 10. 77 (s, 1H).

Dated this 11th (Eleventh day) day of April 2003

(CHERYL PINTO)
Director
Glenmark Pharmaceuticals Limited